Straying from the path in neuro-oncology

Historically, advances in oncologic therapy have been sequential. Changes in treatment have been the result of successive studies, each building on the results of those previously performed. This can be illustrated by Einhorn’s studies in gonadal germ cell tumors1 and Bonnadonna’s studies in breast cancer.2 In contrast, in neuro-oncology, it seems that important findings have not always been incorporated into the design of subsequent trials.

Length of Adjuvant Temozolomide

The pivotal trial by the European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada—EORTC-NCIC CE.3—re-energized the field of neuro-oncology. This was a randomized trial that demonstrated the benefit of 6 cycles of adjuvant temozolomide (TMZ) in the treatment of patients with glioblastoma. Consequently, adjuvant TMZ following combined TMZ and radiation therapy (RT) has become the standard of care for patients with newly diagnosed glioblastoma. The next 2 large upfront phase III studies by the Radiation Therapy Oncology Group—RTOG 0525, evaluating dose intense TMZ,4 and RTOG 0825, evaluating the addition of bevacizumab5—increased the duration of adjuvant TMZ to 12 cycles. Although some question the role of adjuvant TMZ, RTOG 0525 and 0825 were not designed to address this issue, and consequently, an additional variable was introduced. The lack of a consistent adjuvant regimen in large-scale trials leads to variations in the length of adjuvant treatment in clinical practice.6,7 Because no formal investigation of different lengths of treatment with TMZ has been conducted, the utility of longer or shorter treatments is unknown. Certainly prolonged therapy with TMZ is not without toxicity.

Procarbazine, Lomustine, and Vincristine or TMZ

Two other important trials in neuro-oncology were EORTC 269518 and RTOG 9402:9 these studies were launched in the mid-1990s and evaluated procarbazine, lomustine, and vincristine (PCV) combination chemotherapy for patients with newly diagnosed anaplastic oligodendrogliomas. After more than 15 years, they provide remarkably similar results. Both demonstrate the superiority of PCV chemotherapy administered peri-radiation to RT alone in patients with 1p/19q heterozygous codeletion. In codeleted subjects in RTOG 9402, PCV given before RT was associated with a survival benefit of more than 7 years compared with RT alone. In EORTC 26951, with a follow-up of over 12 years, median overall survival had not been reached in the RT + PCV arm; median overall survival in the control RT arm was 9.4 years. Although most patients lacking the codeletion received no benefit from PCV therapy, it was found to be of some utility for those with mutations of isocitrate dehydrogenase.10

Wide adoption of PCV + RT would be presumed, especially in view of the long follow-up in both of these studies. However, perhaps because of the ease of administration or the relatively tolerable side effects of TMZ, an oral alkylating agent, this has not been the case. This is evidenced by the most recent revision of the CODEL study, NCCTG-N0577.11 This trial for patients with 1p/19q codeleted anaplastic gliomas initially opened in 2009 with 3 arms: combined TMZ with radiation, radiation alone, and TMZ alone (see insert below). When the results of EORTC 26951 and RTOG 9402 were reported, accrual to CODEL was suspended. It was subsequently resumed after the trial was amended to include PCV following radiation as a substitute for the RT-only arm. The modified CODEL study, however, retains the third arm—TMZ alone—monotherapy. It is difficult to comprehend how this arm, having neither of the treatments proven in 2 randomized phase III studies, can be presented as an option to patients.

One to 3 Brain Metastases

Lastly, Patchell and colleagues12 have produced level 1 evidence demonstrating survival benefit for surgical resection with a single brain metastasis. Recognizing this, large phase III studies have lumped patients with one brain metastasis with those who have several metastatic lesions and then do not necessarily include surgical resection as an option for patients.13,14
including patients with multiple brain metastases makes it more likely that the study will be completed, it is difficult to rationalize failing to include proven therapy, resection of a single metastasis, as a treatment option.

Conclusion

Over the last 30 years, the treatment of cancer has been, perhaps more than the treatment of any other condition, data driven. So, it is odd that current treatment paradigms in neuro-oncology do not incorporate proven therapies. It may be that this reflects the relatively dismal history of chemotherapy for the treatment of brain tumors. If nothing works well, it is less important what is given. But, recent studies in this population have shown clinically relevant improvements with tested agents. Perhaps it is time to recognize that the therapy that is offered patients with brain tumors can change outcome. And if this is the case, we should act with the same respect for data and expect the same rigor in the development of studies and treatment regimens that we do when dealing with patients who have other types of cancer.

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References


Letter to the editor